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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,797	BRAZZELL ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006 and 02 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8,27-33,38-41,43 and 45-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,27-33,38-41,43 and 45-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/5/2006 and 6/2/2006 have been entered.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claims 1-3, 8, 27-33, 38-41, 43, 45-50 are currently pending and are examined herein.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-3, 8, 27, 28, 30, 31, 43, and 45-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Leboulch et al. (WO 99/26480, cited as IDS reference AN), for the reasons of record (e.g., see the Action mailed on 3/14/05), reiterated below for convenience.

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33). Therefore, Leboulch anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of Keshet et al. (Journal of Clinical Investigation, 1999) and further in view of Otani et al. (Investigative Ophthalmology & Visual Science, 1999) for the reasons of record (e.g., see the Action mailed on 3/14/05), reiterated below for convenience.

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that the method can be used to treat choroidal neovascularization.

Keshet et al. teaches that endostatin is an antiangiogenic peptide that inhibits VEGF activity. Specifically, Keshet et al. teaches, "Endostatin was shown to inhibit VEGF-induced

endothelial cell migration in vitro and to have anti-tumor activity in vivo, without any apparent signs of toxicity." (See p. 1500, 1st column, lines 3-6).

Furthermore, it was recognized in the art that vascular endothelial growth factor (VEGF) is involved in choroidal neovascularization (CN). For instance, Otani et al. teaches,

> "Recent histological and immunohistochemical studies of experimentally produced and surgically excised CNVMs [choroidal neovascular membranes] have indicated that VEGF, transforming growth factor beta (TGFβ), acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF) are involved in the mechanism of CNVM formation associated with ARMD [age-related macular degeneration]. Because VEGF has great selectively for endothelial cells, it is considered to be a critical angiogenic factor in the development of CVMN, even though the mechanism of CNVM is not fully understood." (Emphasis added; see paragraph bridging pages 1912-1913).

It is also noted that Otani et al. teaches, "Present findings that Ang2 and VEGF are co-upregulated and that Tie2 is expressed in a variety of cell types in CVNMs further support a crucial role of the interaction between VEGF and Ang2 in pathologic angiogenesis of CNVM formation." (See p. 1912, Abstract).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the method taught by Leboulch to ameliorate or reduce the rate of choroidal neovascularization in a subject with a reasonable expectation of success.

Since the teachings of the prior art indicate that (1) Endostatin is an antiangiogenic factor that inhibits VEGF activity, (2) Endostatin can be used in gene therapy methods to inhibit neovascularization, and (3) VEGF is known to be involved in choroidal neovascularization (e.g., see Otani et al.) one of ordinary skill in the art would have been motivated to use the method of Leboulch to inhibit choroidal neovascularization.

Claims 1 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,106,826 (Brandt et al.) for the reasons of record (e.g., see the Action mailed on 3/14/05), reiterated below for convenience.

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is administered intravitreally.

Brandt teaches gene therapy vectors which can be used to deliver therapeutic genes for gene therapy, and specifically teaches an HSV vector as well as an adenoviral vector and adeno-associated vector for use in gene therapy of the eye wherein the vector can be delivered to the eye by intravitreally injecting the vector as well as subretinally and intraocullarly delivering the vector, for therapeutic purposes, such as macular degeneration. (e.g., see abstract, column 5, lines 5-20, column 8,lines 57-65, and column 9 lines 15-20).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method taught by Leboulch such that the vector used was delivered intravitreally with a reasonable expectation of success.

The motivation to modify the method of Leboulch is supplied by Brandt who specifically teaches that intravitreal delivery of a therapeutic vector is an effective administration for gene therapy of eye diseases.

Claims 1, 33 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,555,107 (Poeschla et al.) for the reasons of record (e.g., see the Action mailed on 3/14/05), reiterated below for convenience.

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is a lentiviral vector or that that the vector is a bovine immunodeficiency viral vector.

Poeschla teaches methods of gene therapy for the eye wherein a lentiviral vector, specifically a bovine immunodeficiency vector, is used to deliver and express the therapeutic gene in the eye of the subject. (For example, see abstract, column 2, lines 10-35; column 4, lines 34-41; column 11, 45-55).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Leboulch such that the gene therapy vector used is the bovine immunodeficiency viral vector taught by Poeschla (which is a lentiviral vector) with a reasonable expectation of success.

The motivation to make such a modification is provided by Poeschla. Poeschla teaches that the BIV vector is better for transfecting difficult to target non-dividing cells of the nervous system including eye cells.

Claims 1, 33, 38-41 and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,555,107 (Poeschla et al.) and further in view of US Patent 6,106,826 (Brandt et al.) for the reasons of record (e.g., see the Action mailed on 3/14/05), reiterated below for convenience.

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses

endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is a lentiviral vector such as a bovine immunodeficiency viral (BIV) vector or that the lentiviral/BIV vector is administered intraocularly, subretinally or intravitreally.

Poeschla teaches methods of gene therapy for the eye wherein a lentiviral vector, specifically a bovine immunodeficiency vector, is used to deliver and express the therapeutic gene in the eye of the subject. (For example, see abstract, column 2, lines 10-35; column 4, lines 34-41; column 11, 45-55).

Brandt teaches gene therapy vectors which can be used to deliver therapeutic genes for gene therapy, and specifically teaches an HSV vector as well as an adenoviral vector and adeno-associated vector for use in gene therapy of the eye wherein the vector can be delivered to the eye by intravitreally injecting the vector which would necessarily encompass sub-retinal as well as intraocular delivery (e.g., see abstract, column 5, lines 5-20, column 8, lines 57-65, and column 9 lines 15-20).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Leboulch such that the bovine immunodeficiency viral

vector taught by Poeschla (which is a lentiviral vector) is used to deliver and express the therapeutic gene and to deliver the lentiviral/BIV vector by intravitreally, subretinally or intraocullarly injecting the gene therapy vector with a reasonable expectation of success.

The motivation to make such a modification is provided in part by Brandt who specifically teaches that adenoviral and AAV vectors can be used to treat eye disease by intravitreally, subretinally or intraocullarly delivering the therapeutic vector; and in part by Poeschla who teaches that the BIV vector is better for transfecting difficult to target non-dividing cells of the nervous system including eye cells.

Response to Arguments and Declaration

The Dr. Sheila Connelly Declarations under 37 CFR 1.132 filed 2/13/2006 and 5/5/2006 are insufficient to overcome the rejection of claims based upon 35 U.S.C. 102(b) and 35 U.S.C. 103(a) as set forth in the last Office action for the following reasons.

Dr. Connelly indicates that she has read and understands the Leboulch et al. reference (WO 99/26480), and it is her opinion that at the time of filing (February 2001) although endostatin was demonstrated by Dr. Judah Folkman's laboratory in the mid 1990's to be an anti-angiogenic agent that could treat some cancers in mice, "[E]ndostatin rapidly fell out of favor with scientists as they were unable to repeat the studies from Dr. Folkman's laboratory." Dr. Connelly cites a Wall Street Journal article from 1998 entitled "Novel cancer approach stumbles as others fail to repeat success". Dr. Connelly states, "The prevailing attitude at the time was significant skepticism about the therapeutic utility of endostatin." Dr. Connelly asserts that the scientific literature is replete with articles of endostatin failure and cites several articles including

Jouanneau et al. 2001, Eisterer et al. 2002, and Bachelot et al. 2002. Dr. Connelly correctly identifies Dr. Leboulch, an inventor of the WO 97/26480 application, as co-author of the Jouanneau et al., Eisterer et al., and Bachelot et al. references and asserts that Dr. Leboulch was "on the forefront of researchers discrediting endostatin." In her second Declaration Dr. Connelly states, "The prevailing attitude at the time of Leboulch et al. was significant skepticism about the therapeutic utility of endostatin." Dr. Connelly asserts that Leboulch et al. "recognize the unpredictability of having endostatin function for treating cancer, and then provide a generic listing of tissues without any discussion of a particular vector or target cell type, etc." Dr. Connelly also indicates that she was advised that many of the Examples were not actually conducted which leads her to conclude that Leboulch does not provide any information that endostatin is antiangiogenic in the eye.

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion.

(1) In the instant case, the nature of the fact sought to be established is whether or not, at the time the instant application was filed, Leboulch et al. (WO 99/26480) provides an enabling disclosure for ameliorating or reducing the rate of ocular neovascularization in an individual afflicted with ocular neovascularization by administering to the eye or eyes of the individual a viral vector that operably encodes and expresses a functionally active endostatin. It is not required that Leboulch et al. provide an enabling disclosure for using endostatin gene therapy to treat cancer. It is noted that, at the time of filing, (1) endostatin was recognized to be

an anti-angiogenic factor, (e.g., see U.S. Patent 5,8854,205 and 6,174,861), and (2) one of skill in the art would know that there were methods available to deliver and express a therapeutic gene in an eye (e.g., see US Patents 5,827,702, 6,201,104, 6,106,826, and 6,555,107, all previously cited)

(2) There is significant evidence which opposes the conclusion of the Connelly declarations that Leboulch et al. is not enabled for treating ocular neovascularization of the eye by endostatin gene therapy. For instance, U.S. Patent No. 5,854,205 establishes that endostatin is an antiangiogenic protein, and U.S. Patent No. 6,174,861 claims a method of inhibiting angiogenesis by administering endostatin. Furthermore, one of skill in the art would know that there are methods for delivering and expressing therapeutic genes ion the eye (e.g., see US Patents 5,827,702, 6,201,104, 6,106,826, and 6,555,107, all previously cited). Therefore, one of skill in the art aware of the above indicated prior art, would, without evidence to the contrary, consider the teaching of Leboulch et al. that expressing the endostatin gene in an eye of an individual suffering from ocular neovascularization to be enabled.

(3) It appears that Dr. Connelly may have an interest in the case since she is a co-author of a journal article entitled "Intraocular expression of endostatin reduces VEGF-induced retinal vascular permeability, neovascularization and retinal detachment." (FASEB Journal, published Marh 28, 2003). The FASEB article also includes Dr. Campochiaro, Dr. Kaleko and Dr. Luo as co-authors, all of which are also listed as inventors of the instant application. Furthermore, the FASEB article also indicates that Dr. Connelly, Dr. Kaleko and Dr. Luo are all employed by Advances Vision Therapies, Inc.

(4) The articles cited by Dr. Connelly, which provide the factual support for her position, do not indicate that, at the time of filing, Leboulch et al. is not enabled for treating ocular

neovascularization of the eye by endostatin gene therapy. Although Dr. Connelly asserts that the scientific literature is replete with articles of endostatin failure, none of the articles cited by Dr. Connelly provide evidence that indicates that it is unpredictable whether or not endostatin is an anti-angiogenic factor. All of the references cited by Dr. Connelly indicate, at best, that there is inconsistency in using endostatin as an anti-cancer agent. It is respectfully pointed out that at least some of the references cited by Dr. Connelly recognize endostatin as an anti-angiogenic factor.

For instance, Jouanneau et al. teach, "Here, we have evaluated the efficacy of one of the most promising natural inhibitors of angiogenesis described to date, endostatin, in a human neuroblastoma xenograft model in nude mice... The in vitro activity of soluble endostatin was confirmed on bovine capillary endothelial cells and human umbilical vein endothelial cells." (See abstract). Figure 2 of Jouanneau demostrates the in vitro anti-angiogenic activity of endostatin.

Eisterer et al. teach, "A variety of studies have indicated endostatin to be a potent anti-angiogenic agent both in vitro and in vivo, and a human malignancy that might be sensitive to endostatin is human B-lineage acute lymphoblastic leukemia (B-ALL)." (See abstract) Although Eisterer does not teach that endostatin is an effective anti-cancer agent, there is no doubt that Eisterer recognizes the antiangiogenic activity of endostatin.

Bachelot teaches:

> "One of the most promising of these recently described natural inhibitors of angiogenesis is endostatin, a C-terminal fragment of collagen XVIII. In-vitro, endostatin strongly inhibits endothelial cell proliferation and migration. Initial in-vivo studies were impressive, recombinant endostatin was shown to induce regression and prevent the growth of experimental tumors in mice. Several studies by independent teams were published thereafter; they either described different forms of the recombinant protein, or

> developed gene therapy approaches. Most groups have shown perceptible activity in mouse tumor models, albeit without evidence of tumor regression." (Emphasis added, See abstract).

Therefore, Bachelot teaches that most studies have shown perceptible endostatin antiangiogenic activity in mouse tumor models even if evidence of tumor regression was not seen.

Furthermore, U.S. Patents 5,854,205 and 6,174,861 teach that endostatin is an antiangiogenic molecule which can be used to inhibit angiogenesis in a subject. For instance, 6,174,861 explicitly teaches,

> "It is yet another object of the present invention to provide a method and composition for treating diseases and processes that are mediated by angiogenesis including, but not limited to, hemangioma, solid tumors, leukemia, metastasis, telangiectasia psoriasis scleroderma, pyogenic granuloma, myocardial angiogenesis, plaque neovascularization, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy, retrolental fibroplasia, arthritis, diabetic neovascularization, macular degeneration, wound healing, peptic ulcer, fractures, keloids, vasculogenesis, hematopoiesis, ovulation, menstruation, and placentation." (Emphasis added, see column 4, lines 10-23).

It is not clear how Dr. Connelly was advised that many of the Examples in Leboulch were not actually conducted. Furthermore, there is no evidence presented which indicates that that endostatin would not function as an antiangiogenic in the eye.

Therefore, given the very strong evidence indicating that endostatin is an antiangiogenic protein and considering that methods of gene therapy of the eye were taught in the prior art, the conclusion is inescapable that Leboulch et al. provides an enabling disclosure for treating ocular neovascularization of the eye by delivering to the eye a gene therapy vector that encodes and expresses endostatin.

Applicants argue that Leboulch (WO 99/26480) is not enabling for ocular gene therapy, as is required, and thus does not anticipate the instant claims. Applicants cite several court cases in support of their position. For instance, Applicants cite MPEP §2121.01, which indicates that the test for determining whether a prior art disclosure is sufficient and effective is whether the reference contains an enabling disclosure (In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1964). Also, In re Donohue, 766 F.2d 531,226 USPQ 619 (Fed. Cir. 1985) which indicates, a reference is considered to contain an enabling disclosure if the public was in possession of the disclosed subject matter before the date of invention. Such possession is effective if the artisan could have combined the description in the publication with her or his own knowledge to make the claimed invention. Applicants also cite In re LeGriece, 301 F.2d 929, 49 CCPA 1124 (1962) as being instructive on that point. Applicants also cite U.S. v. Adams, 383 U.S. 39, 148 USPQ 479 (1965), Process Control Corporation v. HydReclaim Corporation, 190 F.3d 1350, 52 USPQ 2d 1029 (Fed. Cir. 1999), and In re Cook, 439 F.2d 730, 169 USPQ 298 (CCPA 1971).

All of the cited cases have been reviewed, and the Examiner does not take issue with the notion that a prior art reference must be enabled in order to be considered effective. However, for the reasons indicated herein, Applicants have not provided sufficient evidence to demonstrate that Leboulch et al. is not enabled for ameliorating or reducing the rate of ocular neovascularization in an individual afflicted with ocular neovascularization by administering to the eye or eyes of the individual a viral vector that operably encodes and expresses a functionally active endostatin. The evidence provided by Applicants, at best, indicates that endostatin may not always work as an anti-cancer agent. There is no evidence presented which would bring into question endostatin's ability to inhibit angiogenesis in any tissue, let alone the eye.

Furthermore, it is respectfully pointed out that claim 33 of WO 99/26480 explicitly claims using gene therapy to treat diabetic retinopathy wherein endostatin expression inhibits angiogenesis in the vicinity of the retina. Furthermore, page 2 (last full paragraph) of the WO 99/26480 document clearly teaches ex vivo and in vivo methods and identifies in vivo therapy as a preferred embodiment. WO 99/26480 also indicates that methods preferably involve delivery of the angiogenesis inhibiting polypeptide using a viral vector or plasmid which can be administered so that cells of the patient in the vicinity of the target site are infected or transfected with the nucleic acid encoding the angiogenic-inhibiting polypeptide. Furthermore, like the instant application, the WO 99/26480 document teaches in detail a number of different viral vectors that can be used to deliver and express the therapeutic endostatin protein (e.g., see page 5). The WO document indicates that the term "a gene therapy vector" is meant to mean a vector useful for gene therapy and can be a virus, plasmid or phage (see page 5). The WO 99/26480 document teaches, "preferred vectors include, e.g., retroviral vectors, adenoviral vectors, adeno-associated vectors, herpes virus vectors, Similiki Forest Virus-based vectors, Human Immunodeficiency Virus, Simian Immunodeficiency virus, and non-viral plasmids" (see page 5). Additionally, page 9 of the WO 99/26480 document teaches, in detail, a preferred embodiment in constructing a gene therapy vector that is sufficient for use in the treatment of angiogenesis in vivo. WO 99/26480 also explicitly teaches that the eye is a specific target for the delivery of the therapeutic nucleic acid (e.g., see page 14, lines 1-15). Therefore, WO 99/26480 teaches each and every element of the instant claims. Therefore, the WO 99/26480 document clearly teaches using a vector that expresses endostatin for inhibiting angiogenesis in the eye of a patient

suffering from diabetic retinopathy, and discloses a number of specific vectors and methods of administration for accomplishing the treatment.

Furthermore, the Applicants have not indicated any specific critical element that the WO 99/26480 document fails to teach which prevents the document from providing an enabling disclosure. For instance, evidence that endostatin does not inhibit angiogenesis in the eye would indicate that Leboulch et al. is not enabled.

It is acknowledged that the WO 99/26480 document does not disclose a working example for the indicated method. However, in view of the state of the prior art with respect to gene therapy of the eye as well as the state of the art with respect to using endostatin as an anti-angiogenic factor in protein and gene therapy, the WO 99/26480 document does provide a sufficient disclosure to enable the indicated method.

Therefore, Applicants arguments are not persuasive and the rejections are maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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